Ralph de Vere White Symposium for Early-Stage Investigators in Cancer

PRESENTATION ABSTRACTS

Oral Presentations

#1 SINGLE-CELL RESOLUTION IMPACT OF RADIATION THERAPY ON MURINE SQUAMOUS CELL CARCINOMAS IN VITRO REVEALS MECHANISMS BEHIND RESISTANCE

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Abstract
Patients with advanced head and neck squamous cell carcinoma (HNSCC) have poor prognosis in part due to insufficient anti-tumor immune responses. Unfortunately, immunotherapy has poor efficacy in treating HNSCC, perhaps because tumor antigen is not detected by immune cells. Adding radiation therapy (RT) to immunotherapy improves tumor clearance by increasing tumor antigen presentation in only a fraction of HNSCCs. To study this, our lab previously generated two spontaneous mouse SCC cell lines that differed in their response to RT in the context of immunotherapy treatment: “RT-sensitive” cell line or “RT-resistant” cell line. Since these models were spontaneously derived, we sought to determine the mechanisms behind RT-resistance with the hope that findings will apply to human patients. To do so, we conducted an in vitro experiment where mouse SCC cells were treated with or without 10 Gray RT and incubated for 48 hours prior to single cell RNA sequencing. Clustering revealed 5 cell phenotypes – dividing, epithelial-like, mesenchymal-like, neuron-like, and interferon response – within both cell lines. Radiation therapy significantly altered the composition of the SCC cultures in different ways. In some ways, RT effected both cell lines similarly: for example, RT upregulated genes related to DNA repair in both cell lines. However, RT had additional effects on RT-sensitive cells only, promoting interferon response gene expression as well as a shift towards the mesenchymal phenotype. In total, these results suggest that RT-resistant HNSCCs avoid cell death by preventing the upregulation interferon and mesenchymal gene expression programs. Future studies should determine the mechanisms by which RT-resistant HNSCCs suppress these programs to avoid cell death. Further, these mechanisms should be investigated in human HNSCCs with the goal of informing patient selection and designing rational combination therapies.

Lay Abstract
I study the impact of radiation therapy on head and neck tumors with the specific goal of improving radiation therapy efficacy. Radiation therapy has broad effects on tumors besides killing cancer cells. For example, radiation therapy may stimulate our immune system to kill cancer cells. However, some tumors respond to radiation therapy while others do not -- my thesis project focuses on why this is the case. Furthermore, I hope to design a combination therapy combining radiation therapy with immunotherapy to address resistance to radiation therapy and improve head and neck cancer patient survival.

#2 DIFFERENCES IN TREATMENT AND SURVIVAL FOR SECONDARY TRIPLE NEGATIVE BREAST CANCER IN PREMENOPAUSAL WOMEN

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Abstract
Background: Women diagnosed with a secondary triple negative breast cancer (TNBC) have worse overall survival (OS) and breast cancer specific survival (BCSS) compared to those with a primary TNBC. There are currently no guidelines on how to treat a secondary TNBC. We aim to identify and differentiate the treatments used for secondary vs primary TNBC and evaluate for associated survival differences.

Methods: Using the California Cancer Registry, women aged 15-50 years, diagnosed from 2003-2019 with a primary TNBC (N= 9220) or secondary TNBC (N=682), defined as a new TNBC after any prior cancer, were included. We compared treatments for secondary vs. primary TNBC using multivariable logistic regression and examined OS and BCSS with multivariable Cox proportional hazards regression models.

Results: Secondary TNBCs were more commonly treated with no chemotherapy (none, 27.3%) or non-anthracycline (vs anthracycline) based regimens, with Taxotere + Cyclophosphamide (TC, 23.9%) being most common. Less women with a secondary TNBC received radiation (28%) compared to those with a primary TNBC (48.4%). Women with a secondary TNBC were two-times more likely to undergo a mastectomy (vs lumpectomy) [odds ratio (OR) 2.02 (95% confidence interval (CI): 1.62, 2.51)]. Women with secondary TNBC had worse OS with TC [hazard ratio (HR) 1.69, CI: 1.12, 2.55)] or no chemotherapy [HR 1.56 (CI: 1.09, 2.23)], but there was no difference in BCSS seen by treatment type compared to women with primary TNBC.

Conclusions: Significant differences were noted between the treatments for primary TNCs and secondary TNBCs, with the key difference being the decreased use of chemotherapy in women with a secondary TNBC. This, in addition to the use of a non-anthracycline based regimen, could be related to the worse overall survival seen in women with a secondary TNBC. Our findings suggest further exploration into the decisions for chemotherapy, such as the consideration for chemotherapy at earlier stage disease in secondary TNBC.

Lay Abstract
It has been shown that women who are diagnosed with a triple negative breast cancer as a secondary cancer have worse survival. The focus of this research was to identify what treatments (surgery, chemotherapy, radiation) were being used to treat triple negative breast cancer when diagnosed as a secondary cancer and to see if these treatments were different than those used for triple negative breast cancer as a primary cancer. We then evaluated if the worse survival seen with secondary triple negative breast cancers was associated with the differences in treatment types between the two cancers.

#3 IGFBP3-MEDIATED SPHK1/S1P SIGNALING DRIVES ENZALUTAMIDE RESISTANCE IN ADVANCED PROSTATE CANCER

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Abstract
Enzalutamide resistance remains a significant challenge in the treatment of advanced prostate cancer. Identifying molecular drivers of enzalutamide resistance is crucial for developing effective therapeutic strategies. In this study, we identify insulin-like growth factor binding protein 3 (IGFBP3) as a key driver of enzalutamide resistance in castration-resistant prostate cancer (CRPC). Using RNA sequencing and gene set enrichment analysis (GSEA), we demonstrate that IGFBP3 expression is significantly upregulated in enzalutamide-resistant C4-2B MDVR cells compared to parental C4-2B cells. This upregulation was consistently observed across multiple enzalutamide-resistant CRPC models, including LNCaP-derived 42D and 42F cells, as well as long-term enzalutamide-resistant cell lines derived from LNCaP, VCaP, LAPC-4, and CWR-R1 cells. Additionally, Enzalutamide treatment directly induced IGFBP3 expression in sensitive cells. Elevated IGFBP3 expression was also observed in CRPC patient samples post-enzalutamide treatment and was associated with higher Gleason scores and reduced disease-free survival. Mechanistically, IGFBP3 activates the sphingosine kinase 1 (SphK1)/sphingosine-1-phosphate (S1P) signaling pathway, which promotes cell survival and resistance to enzalutamide. IGFBP3 knockdown decreased SphK1 expression, reduced S1P secretion, and enhanced enzalutamide sensitivity, whereas IGFBP3 overexpression induced SphK1 expression and S1P production, conferring enzalutamide resistance. Inhibition of IGFBP3 via siRNA reduced cell viability, induced apoptosis, and re-sensitized resistant models to enzalutamide. Similarly, targeting SphK1 with the inhibitor SKI-II suppressed SphK1 activity, reduced S1P production, enhanced enzalutamide sensitivity in vitro, and significantly inhibited resistant tumor growth while enhancing enzalutamide sensitivity in vivo. Collectively, these findings highlight IGFBP3-mediated SphK1 signaling as a critical mediator of enzalutamide resistance and suggest that targeting the IGFBP3/SphK1/S1P axis represents a promising therapeutic strategy to overcome resistance in advanced prostate cancer.

Lay Abstract
Androgen receptor signaling inhibitors (ARSI), such as enzalutamide, have significantly improved clinical outcomes for patients with CRPC. However, resistance to enzalutamide frequently emerges, limiting its long-term efficacy and contributing to disease progression. Understanding the molecular mechanisms underlying enzalutamide resistance is therefore critical for the development of novel therapeutic strategies to enhance treatment response and improve patient outcomes. In this study, we examine the role of IGFBP3 in enzalutamide-resistant prostate cancer models and explore its functional link to SphK1/S1P signaling. We provide evidence that IGFBP3 is upregulated in enzalutamide-resistant cells and CRPC patients. Furthermore, we demonstrate that targeting IGFBP3 or SphK1 can restore enzalutamide sensitivity. These findings highlight a novel mechanism of enzalutamide resistance and suggest potential therapeutic interventions to improve prostate cancer treatment outcomes.

#4 DEVELOPMENT OF NANOBODY-BASED THERAPY FOR OSTEOSARCOMA

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Abstract
Osteosarcoma (OS) is the most common malignant tumor in the skeletal system. Novel treatments like antibody-drug conjugates (ADCs), which utilize antibodies to deliver therapeutic drugs to tumor cells specifically, have been tested for OS but have shown inefficient. A possible reason could be the very dense extracellular matrix of OS cells, which can prevent the penetration of ADCs, and the low specificity of OS cell surface markers used for current ADCs. Our lab

specializes in the characterization of skeletal stem cells and their downstream lineages, which can guide us to distinguish the OS cells from normal skeletal stem cells by cell surface markers. Nanobodies are promising alternatives for antibodies in ADCs due to their significantly smaller size. We hypothesize that with more specific cell surface markers and nanobodies, we can develop more efficient targeted therapies for OS. To test our hypothesis, we engineered an OS cell line (SAOS2) by labeling the cell membrane, which can be recognized by anti-GFP nanobodies. In vitro and in vivo assays were done to test the nanobodies on cancer cells. A co-culture of GFP-labeled and non-labeled tumor cells was generated to test if the nanobodies could specifically bind to GFP-SAOS2 cells, and was validated through fluorescence-activated cell sorting (FACS). An OS mouse model was created that contains WT and GFP-labeled tumors. The OS mouse model was developed to assess the in vivo penetration and retention of nanobodies. We observed that the anti-GFP nanobodies specifically bind to GFP-labeled OS cells in the co-culture system. The mouse models showed that anti-GFP nanobodies have high affinity and retention in GFP-labeled tumors. The results prove the concept of ADCs using nanobodies as a therapy for OS. The nanobody-targeted therapy can be applied to other tumors and shows the strength of a new class of ADCs.

Lay Abstract

Osteosarcoma is a common bone cancer that primarily affects young adults during puberty. Since the cancer is surround by bone and its dense matrices, normal therapies have a difficult time being delivered to the cancer. Nanobodies are very small antibodies that are able to overcome this barrier and could deliver anti-cancer therapies to osteosarcoma. We performed a proof of concept to show that nanobodies can be used as an alternative treatment for osteosarcoma.

#5 TARGETING PANCREATIC CANCER LIVER METASTASES USING REGIONAL NK CELLULAR THERAPY AGAINST B7-H3

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Abstract

Pancreatic adenocarcinoma (PDAC) is an aggressive malignancy characterized by early liver metastases. Though promising, natural killer (NK) cell therapies have had limited success in solid tumors. We set out to evaluate the function of placental-derived NK cells (PL-NK) in combination with a B7-H3 engaging antibody. We also investigated the effect of portal vein delivery as a method to enhance liver engraftment with the goal of combining regionally delivered PL-NK cells with B7-H3 targeting to treat PDAC liver metastases.

B7-H3 staining was performed on patient PDAC samples. NK cells were isolated from human placenta and expanded using K562.Cl9 feeder line and IL-2. Phenotype was evaluated by flow cytometry and functional assessment by PANC-1 killing assays. Nanoparticle-labelled NK cells were adoptively transferred into NSG mice via tail vein (IV) or portal vein (PV) injection and engraftment was assessed by ultrasound-guided photo-acoustic imaging and flow cytometry. Liver metastatic PDAC was recapitulated using the hemi-spleen model with PANC-1 cells.

B7-H3 expression was detected on 90% (76/84) of primary PDAC samples and PANC-1 cells had 97% positivity in vitro. PL-NK cells showed cytotoxicity against PANC-1 cells over 24 hours in vitro. Addition of the B7-H3 TriKE significantly enhanced killing at all time points ($P<0.05$). 24 hours after NK cell administration, in vivo liver imaging detected a 2.7-fold higher signal from PV compared to IV and confirmed by flow cytometry with PV having higher human CD45+ cells in the liver (23.6% ± 7.6 vs 8.8% ± 4.5, $P = 0.03$). Injection of PANC-1 into hemi-spleen mice resulted in isolated liver metastases within 50 days in all mice injected.

B7-H3 represents a viable immunotherapy target for PDAC. PL-NK kill PANC-1 cells and this is enhanced by B7-H3 engagement. PV administration results in increased liver engraftment and is being investigated as a strategy for targeting PDAC liver metastases in animal models.

Lay Abstract
Our lab focuses on treating pancreas cancer that has spread to the liver using engineered immune cells. We are looking at new ways to give these therapies that are more effective at killing cancer cells while also being safer for patients.

#6 UNDERSTANDING CANINE ORAL NEOPLASIA: INTRINSIC RATHER THAN EXTRINSIC FEATURES REPRESENT KEY RISK FACTORS IN A 39-YEAR ANALYSIS

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Abstract
Canine oral neoplasia is often detected late in the course of the disease, necessitating radical surgeries frequently combined with adjuvant chemotherapy or radiotherapy for positive outcomes. Although there has been extensive analytical and epidemiologic work on human oral cancer, research in veterinary medicine has been lacking. This study aimed to evaluate the prevalence and risk factors associated with canine oral neoplasia to enhance early detection by improving screening Patient data from 1985 to 2024 from the University of California-Davis Veterinary Teaching Hospital were bulk extracted to determine prevalence as well as the effect of clinical and environmental risk factors, including sex, breed, oral location, air quality, and periodontal disease status. The median air quality index (AQI) data were extrapolated from the Environmental Protection Agency's database. Periodontal disease status was evaluated on patient CT scans. The incidence of oral tumors was 4.59/1,000 patients. The median age upon diagnosis was 9.66 years, and 3 breeds were identified as significantly at risk compared to the general patient population. Air quality index, geographical location, and periodontal disease were not associated with oral neoplasia. Different tumor histologies had distinct oral predilection sites. Overall, there was a significant correlation between age/breed and oral neoplasms. Tumor locations were significantly different for each pathology. Other risk factors did not play a substantial role in disease. These findings can aid veterinarians and researchers in targeting screening and treatment strategies in high-risk dogs.

Lay Abstract
We have analyzed several risk factors from the UC Davis veterinary hospital's database, such as age, sex, breed, dental health, and geographical location. We investigated the type of cancer and its location within the dog's mouth. Overall, we found that external risk factors, such as air quality, home address, and dental disease were insignificant between the oral cancer and general canine population. However, there was a correlation between age/breed and oral cancer. Our findings can help general practice veterinarians better allocate their time during routine oral cancer screenings based for at-risk patients.

#7 DEVELOPING TOBACCO TREATMENT SUPPORT WITH COMMUNITY HEALTH WORKERS USING A CARE NAVIGATION PLATFORM

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Abstract
Background: Community Health Workers (CHWs) are trusted members of their communities who can help improve engagement with populations for cancer prevention. Implementing CHW services is still in development as a relatively new Medi-Cal benefit. CHWs are a promising channel to increase tobacco treatment, as Medi-Cal's Latino members receive less quit advice from health professionals compared to non-Latino White counterparts.
Objective: This study describes the implementation plans for CHWs to use the Pear Suite care navigation platform to expand tobacco cessation services for Health Net Medi-Cal members.

Methods: We use Consolidated Framework for Implementation Research (CFIR) to describe the development and implementation of the pilot intervention in the Central Valley.

Results: The intervention adapted a quitline referral protocol from 211 county services into Pear Suite's digital platform, enabling CHWs to deliver tobacco cessation support. Collaborative leadership from Pear Suite and Health Net, along with pilot funding support from the Tobacco Cessation Policy Research Center (TCPRC) and California Health Care Foundation facilitated implementation readiness by ensuring dedicated resources, stakeholder engagement, and streamlined access to training and digital tools. Healthcare Effectiveness Data Information Set, tobacco quality measures, health equity priorities and quitline engagement goals shaped the implementation context. In partnership with Dr. Marcia Tan, UC Davis provided specialized training to CHWs, enhancing their capacity to deliver culturally responsive tobacco cessation support. Key components included adapting Dr. Tan's CHW tobacco cessation training, existing infrastructure and new TCPRC funding for Pear Suite's protocol integration and the development of a real-time data dashboard for quitline referral tracking. The implementation process, guided by CFIR constructs, laid the groundwork for future evaluation using the RE-AIM framework to assess feasibility, acceptability, and impact on quitline engagement and tobacco cessation.

Conclusion: This innovative project seeks to demonstrate how a sustainable CHW model can reduce tobacco treatment disparities among underserved communities in the Central Valley. By equipping CHWs with the tools and training necessary for quitline referrals, this approach offers a scalable solution to advance cessation equity. The findings will be shared with local and state stakeholders and Medi-Cal leadership to inform future efforts in reducing tobacco treatment disparities.

Lay Abstract
This study addresses tobacco cessation disparities among underserved Medi-Cal members by empowering Community Health Workers (CHWs) using the Pear Suite care navigation platform. CHWs, trusted members of underserved communities, received specialized training and a standardized quitline referral protocol adapted from 211 county services. CHWs engaged Medi-Cal members over the phone, in-person and at community events. The pilot project is in progress and will demonstrate the feasibility and acceptability of a CHW-led intervention to increase quitline engagement among Medi-Cal members who speak English or Spanish and live in the Central Valley. This innovative approach highlights the potential of CHWs and digital tools to improve access, reach, and equity in tobacco treatment services.

Poster Presentations

#1 DECIPHERING THE ROLE OF BRD2 IN ACUTE ADAPTIVE RESPONSE TO BET INHIBITORS ACROSS CANCERS

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Abstract
Bromodomain and extraterminal motif (BET) inhibitors, such as JQ1, are a promising therapeutic strategy against cancer, targeting key epigenetic regulators, particularly BRD4. However, resistance to BET inhibitors poses a significant challenge, necessitating a deeper understanding of adaptive mechanisms. Here, we identified the upregulation of BRD2, another member of the BET protein family, as a conserved response to BET inhibition across multiple cancer types. We hypothesize that this upregulation facilitates cellular adaptation to treatment, reducing drug efficacy and potentially contributing to resistance over time. To test this, we performed BRD2 knockdown, demonstrating that BRD2 depletion sensitizes pancreatic cancer cells to BET inhibitors in vitro. Furthermore, a combination of BRD2 knockdown with JQ1 treatment significantly impaired tumor growth in vivo. Mechanistically, ChIP-seq analysis of BRD2 and BRD4 occupancy upon JQ1 treatment revealed that BRD2 and BRD4 share common binding sites. JQ1 caused a substantial loss of BRD4 from chromatin, while BRD2 was modestly affected. Although JQ1 has a higher affinity for BRD4 than for BRD2, our data suggest that higher cellular abundance of BRD2 compensates for BRD4 function under BET inhibitor treatment, thereby contributing to adaptive resistance and sustaining essential transcriptional programs. These findings highlight BRD2 as a key player in the adaptive response to BET inhibition and a potential therapeutic target to enhance the efficacy of BET inhibitors in pancreatic cancer and other malignancies.

Lay Abstract
My research explores how changes in gene regulation—known as epigenetics—influence cancer progression and treatment resistance, particularly in pancreatic cancer. Even without altering the DNA sequence, cancer cells can switch certain genes on or off to help them survive therapy. I study how these epigenetic changes happen and how they might be reversed. By understanding these hidden layers of control, my work aims to uncover new ways to treat cancer more effectively and prevent it from coming back.

#2 POTENTIAL LYSOSOME AND MITOCHONDRIAL INTERACTIONS IN HEXAMETHYLENE AMILORIDE-MEDIATED NECROSIS PATHWAY

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Abstract
Hexamethylene amiloride (HMA) is a cationic amphiphilic drug that has been linked to selectively targeting tumor cells and inducing cancer cell death. A gap exists in the use of current cancer therapies (including chemotherapy, radiation, and immunotherapy), which each have a plethora of side effects and demonstrate ineffectiveness in individual cases for tumors that have developed immunity. In conjunction with the common cancer therapeutics currently in use, HMA has the capacity to become a novel therapy with minimal side effects. This project intends to uncover the mechanism by which HMA induces cell necrosis and whether this mechanism could be via the induction of membrane permeabilization. Through cell fluorescence microscopy on HMA-treated breast cancer cell lines, HMA-induced necrosis via lipid peroxidation can be colocalized to the lysosome, mitochondria, and/or plasma membrane. Quantification of lipid peroxidation pre and post-treatment as well as cross-correlation with the mentioned organelles in the cells treated allow for conclusions to be drawn about how HMA truly works. Further analysis of HMA and its cytotoxic effects have the

potential for optimized drug development, so that it may be used as a cancer therapeutic and aid in the fight against drug-resistant tumors.

Lay Abstract

Chemotherapy, radiation, and immunotherapy are different common treatment options for patients; however, a commonality between them is that they do not work on all patients. Some patients have resistant tumors that are difficult to target. One drug called hexamethylene amiloride (HMA) has been showed to effectively kill breast cancer cells in high concentrations in some trials, but scientists are unsure of how exactly this process is occurring. If scientists knew the mechanism behind which HMA kills cancer cells, they could optimize the drug so that it can be used in lower concentrations in clinical trials on patients. Scientists predict that HMA uses a death pathway that involves breaking down membranes of organelles within the cells - particularly the plasma membrane, lysosome, and/or mitochondria. This project intends to determine which one of these organelles (or what combination of them) break down upon administration of HMA in order to better understand it.

#3 C6 GLIOMA-DERIVED SOLUBLE FACTORS SUPPORT MICROGLIAL SURVIVAL

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Abstract

Significance. Glioma is one of the most fatal primary brain tumors, known for its aggressive invasion into brain tissue. Glioma-associated microglia (GAMs) and macrophages, comprising up to 50% of the tumor mass, are thought to promote tumor progression. Although GAMs infiltrate glioma tissues, how glioma cells influence microglial behavior and survival remains unclear. In this study, we investigated whether soluble factors secreted by glioma cells support microglial viability in vitro. Using a conditioned medium approach, we cultured primary microglia in media collected from glioma cell cultures. Our results demonstrate that glioma-conditioned medium sustains microglial viability in the absence of exogenous survival factors (e.g., IL-34), suggesting that glioma cells secrete soluble factors that promote microglial survival. These findings highlight a paracrine signaling mechanism by which glioma cells modulate the tumor-associated immune microenvironment and provide a foundation for identifying glioma-derived molecules that support microglial persistence.

Materials & Methods. To collect rat C6 glioma cell-conditioned medium, C6 cells were cultured in T-25 flasks with Ham's F-12K medium supplemented with 10% fetal bovine serum (FBS) until confluent. The medium was collected, filtered, and stored at –20 °C. Dissociated cortical cells from neonatal Sprague-Dawley rat pups were seeded onto multi-well plates and maintained in two conditions until day-in-vitro (DIV) 7. One group was cultured in Neurobasal A with B-27 and fresh F-12K with 10% FBS. The other group was cultured in Neurobasal A with B-27 and C6-conditioned F-12K medium. At DIV 7, cultures were fixed and immunostained for Iba1 to visualize microglia. Statistical comparison was performed using Student's t-test.

Results. The group treated with glioma-conditioned medium maintained a significantly higher number of microglia compared to the control group ($p < 0.0001$), suggesting that glioma-secreted factors support microglial survival.
Future directions. To identify the soluble factors supporting microglial survival, cytokine profiling of C6 glioma-conditioned medium will be performed. This analysis may reveal key signaling molecules involved in glioma–microglia communication. Additionally, future studies will examine microglial infiltration into the glioma microenvironment using micropatterned islets of C6 cells surrounded by healthy cortical neurons, offering insights into their recruitment and roles in tumor progression.

Lay Abstract
Glioma is a deadly brain cancer that grows quickly and invades nearby brain tissue. In this tumor environment, immune cells called microglia are often found in large numbers. Scientists believe these cells may actually help the tumor grow. In our study, we looked at whether the cancer cells release substances that help microglia survive. We found that when microglia are grown in a solution collected from glioblastoma cells, they stay alive even without other support. This suggests the cancer is actively helping these immune cells survive. Learning more about how this happens could lead to better ways to treat glioblastoma by targeting the relationship between the tumor and the immune system.

#4 TARGETING CDK11 IN MALIGNANT RHABDOID TUMOR OF THE KIDNEY

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Abstract
Introduction: Malignant rhabdoid tumor of the kidney (RTK) is a rare, aggressive pediatric renal malignancy with an extremely poor prognosis. Tumor progression, treatment resistance, and relapses are common despite treatment, necessitating a search for new therapeutic targets. Rhabdoid tumor genetic analysis show dysfunctions in cell cycle, cell proliferation, and RNA splicing. Cyclin dependent kinase 11 (CDK11) is a protein kinase involved in these processes and its over-expression is associated with various cancers. CDK11 is a potential therapeutic target, and OTS964 is a CDK11 inhibitor. Navitoclax is a Bcl-2 inhibitor which regulates apoptosis. Our study evaluated CDK11 targeting alone and in combination with navitoclax for RTK therapy.

Methods: CDK11 protein expressions were confirmed and measured in two RTK cell lines G401, JMU-RTK-2, and human embryonic kidney cell line HEK293 by qRT-PCR and Western blotting respectively. Drug efficacy of OTS964, doxorubicin, vincristine, and navitoclax was measured in G401 and JMU-RTK-2 via SRB assay. Doxorubicin and navitoclax were also tested for in vitro combination synergy with OTS964. Mechanism of OTS964 treatment was assessed via Western blotting of cleaved PARP, cleaved caspase-3, and p53. In vivo efficacy of OTS964, navitoclax, and combination (OTS964 + navitoclax) was tested using JMU-RTK-2 xenograft mice.

Results: CDK11 protein expression were higher in RTK cells G401 and JMU-RTK-2 than in HEK293 ($p = 0.05, 0.13$, respectively). OTS964 demonstrated significant cytotoxicity in G401 and JMU-RTK-2 cells with IC50 40.04 nM and 19.6 nM at 48 hours after treatment, respectively. Cleaved PARP, cleaved caspase-3, and p53 apoptosis proteins increased after OTS964 treatment. OTS964 combined with doxorubicin or navitoclax showed additive and synergistic effect, respectively. JMU-RTK-2 xenograft mice treated with OTS964, navitoclax, and combination all significantly suppressed tumor growth at 14 days ($p < 0.01$) and end of study ($p < 0.05$). Only monotherapies significantly prolonged survival ($p < 0.05$).

Conclusion: OTS964 showed significant cytotoxicity in RTK cell lines, increasing p53 activation and inducing apoptosis via caspase-3. Single drug and combination therapy significantly decreased tumor volume growth in RTK xenograft mouse model. This study demonstrates the potential of CDK11 inhibition alone and in combination with several drugs, including navitoclax, for RTK therapy.

Lay Abstract
Malignant rhabdoid tumor of the kidney (RTK) is a rare and aggressive childhood kidney cancer. Children with RTK have extremely poor outcomes since tumors continue to grow even with various intensive treatment and the cancer tend to relapse. Based on our understanding of the genetic abnormalities in RTK, targeting the protein kinase CDK11 may be a new potential treatment. This study tested OTS964, a CDK11 inhibitor, alone or in combination with other drugs in RTK cell lines and mice models to evaluate its therapeutic potential. The RTK cell lines G401 and JMU-RTK-2 demonstrated significant cytotoxicity at 48 hours after treatment. Synergy was found when combining OTS964 with the drug navitoclax

and was subsequently chosen for mice model treatment. JMU-RTK-2 tumors grown on nude mice treated with OTS964, navitoclax, and combination all significantly suppressed tumor growth at 14 days ($p < 0.01$) and at end of study ($p < 0.05$). Only monotherapies significantly prolonged survival ($p < 0.05$). These findings highlight the therapeutic potential of CDK11 inhibition alone or in combination in treating RTK.

#5 THE IMPACT OF INSURANCE TYPE ON RECEIPT OF GUIDELINE-CONCORDANT THERAPY AMONG PATIENTS WITH INVASIVE BREAST CANCER

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Abstract
Background: Lack of adequate insurance is a barrier to accessing timely and appropriate breast cancer treatment. In this study, we sought to describe the impact of different insurance types on the receipt of guideline-concordant breast cancer therapy among California women diagnosed with invasive breast cancer.

Methods: The study included women aged ≥18 years who were diagnosed with invasive breast cancer from 2014 to 2022 and identified through the California Cancer Registry (n=200,080). Guideline-concordant breast cancer treatment was defined by these Commission on Cancer quality measures: 1. Receipt of breast-conserving surgery (BCS) or mastectomy for patients with AJCC stages I or II cancers; 2. Receipt of radiation within one year of diagnosis for women under 70 years who received BCS; 3. Radiation therapy within one year of diagnosis for patients with ≥4 positive regional lymph nodes following mastectomy. Multivariable logistic regression was used to assess the association of insurance type (private, Medicaid, Medicare) with the receipt of the quality measures, adjusted for potential confounders. Results are reported as adjusted odds ratios (OR) by age group (≤64 years, ≥65 years).

Results: Adherence to each guideline concordant treatment was highest for measure 1 (95-96%), followed by measure 2 (76%) and measure 3 (50-56%). Among those ≤64 years (n=118,735), patients with Medicaid (n=20,161) or Medicare (n=6,205) (vs. Private insurance (n=87,069)) were less likely to receive all guideline-concordant treatments (ORs: 0.52-0.68). Among those ≥65 years (n=81,345), patients with Medicaid (n=2,577) or Medicare (n=35,515) (vs. private (n=20,632)) were less likely to receive measures 1 or 2 (ORs: 0.54-0.88). However, for measure 2, women with Medicare with supplemental insurance (n=19,396) and private insurance had similar adherence. Adherence to measure 3 did not differ by insurance type in women ≥65 years.
Conclusion: Insurance-related disparities impact access to evidence-based local therapy for breast cancer, with publicly insured patients facing the greatest barriers. While Medicare insurance has improved access to care for older adults, disparities still exist, highlighting the need for addressing these insurance-related disparities to ensure appropriate and equitable cancer care for all patients.

Lay Abstract
Access to health insurance plays a crucial role in ensuring that breast cancer patients receive the recommended treatments in a timely manner. This study examined over 200,000 women in California diagnosed with invasive breast cancer between 2014 and 2022. Our findings show that women with Medicaid or Medicare were less likely to receive guideline-based treatments compared to those with private insurance. Disparities were more pronounced among younger women, while older patients, especially those with Medicare, had improved access. These findings highlight the need to address insurance-related barriers to ensure all patients receive high-quality breast cancer treatment.

#6 IMPACTS OF ELESCLOMOL-INDUCED CUPROPTOSIS ON THE HNSCC TUMOR IMMUNE MICROENVIRONMENT

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Abstract
Head and neck squamous cell carcinoma (HNSCC) is the sixth most common cancer in the world; patients have a 66% 5-year survival rate and have the second highest rate of suicide amongst cancer survivors. Despite modern advancements, the poor prognosis has been slow to improve in part due to immunotherapy resistance and immunosuppressive tumor microenvironment. Cuproptosis, induced by elesclomol, is a novel regulated cell death (RCD) that has anti-tumor effects in breast and hepatic cancer models but has yet to be proven effective in immunotherapy-resistant cancers such as HNSCC. Preliminary data indicates that elesclomol effectively killed SCC cells in vitro while splenocytes were unaffected. Due to its effectiveness in vitro, we hypothesized that elesclomol would be effective in our previously generated immunotherapy-resistant, metastatic syngeneic SCC murine model P029. Tumors were inoculated subcutaneously and allowed to establish before treating with either vehicle or elesclomol/CuCl2 intraperitoneally. We found that the tumor volume and histological analysis of lung metastases necrotic regions were all unaffected by elesclomol treatment when compared to vehicle in P029-inoculated mice. Interestingly, the ratio of circulating neutrophils to lymphocytes in the blood was found to be significantly increased in the treatment group ($P = 0.02060$), indicating a systemic inflammatory response. We also found that the results of Fisher's exact test ($P = 0.0216$) revealed a significant association between elesclomol treatment and ulcer scab formation and closure. Furthermore, immunohistochemistry stains of tissue sections revealed an influx in CD11b+ cells in the treated group ($P = 0.0009$). These findings indicate that while cuproptosis induced by elesclomol does not reduce tumor volume in treatment-resistant SCC, there may be an immune-altering effect whether directly or indirectly through cuproptosis. Elesclomol as a single agent may not be sufficient in treating resistant HNSCC, but it further emphasizes the importance of understanding immune-implicated therapy resistance and the potential for a combination immunotherapy approach. (This study was funded by CO HNC SPORE P50 CA261605)

Lay Abstract
Head and neck cancer is one of the most common cancers worldwide, but treatments haven't significantly improved survival rates in recent years. Many patients don't respond to immunotherapies, a promising new type of cancer treatment, due to changes in the tumor environment that weaken the immune response. My research explores a new type of cancer cell death called cuproptosis, triggered by a drug called elesclomol. While this method has shown promise in other cancers, it hasn't been studied in treatment-resistant head and neck cancers.
We tested whether elesclomol could shrink tumors in a mouse model of advanced, immunotherapy-resistant cancer. Although the drug didn't reduce tumor size or spread, we observed immune system changes suggesting that elesclomol may affect how the body responds to the tumor. Treated mice showed signs of inflammation and shifts in certain immune cells.

These findings suggest that while elesclomol alone may not be enough to treat this aggressive cancer, it could still contribute to combination therapies. Ultimately, this research helps us understand why some head and neck cancers resist treatment—and how we might overcome that resistance. Our overall goal in the lab is to better understand head and neck cancer and improve both existing and emerging therapies.

#7 CONTRAST-ENHANCED CT AS A NON-INVASIVE METHOD FOR ESTIMATING LUNG SHUNT FRACTION IN YTTRIUM-90 LIVER RADIOEMBOLIZATION

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Abstract
Yttrium-90 (90Y) is a radioactive isotope used in radioembolization, a catheter-based therapy that delivers radiation to liver tumors through the liver arteries. In 90Y radioembolization, accurate lung shunt fraction (LSF) estimation is critical to prevent radiation-related lung damage. LSF is the proportion of injected microspheres that bypasses the liver and ends up in the lungs due to abnormal blood vessels. It is usually measured using 99m Tc-macroaggregated albumin (99m Tc-MAA) imaging, which involves an interventional radiology (IR) procedure with intra-arterial injection and nuclear imaging, adding both cost and complexity to treatment planning. This study investigates whether contrast-enhanced computed tomography (CECT) done pre-treatment can be used to estimate LSF non-invasively.

Analysis was performed on 30 liver cancer patients who had both 4-phase CECT and 99m Tc-MAA imaging before treatment, based on the assumption that arterio-venous shunting, which contributes to elevated LSF, results in hypervascularization with increased contrast during the arterial phase of CECT. Subtracting the portal phase from the arterial phase allows the hypervascular regions to be isolated and their volumes to be calculated relative to the perfused liver volume. Non-perfused necrotic tissue was excluded to improve accuracy.
The hypervascular-to-perfused volume ratio derived from CECT strongly correlated with LSF values from “99m Tc-MAA planar imaging (R^2 = 0.95), with a prediction uncertainty of ±3%. Tumor volume showed a poor correlation with LSF (R^2 = 0.38), meaning that the vascular behavior of the tumor is more important than tumor size.

This method can simplify treatment planning by eliminating the need for additional nuclear imaging, injections, and interventional radiology. The CECT-based approach offers a less invasive, more accessible alternative for LSF estimation and provides more efficient care for patients undergoing 90Y liver radioembolization.

Lay Abstract
The research project is about improving how we plan liver cancer treatment with Yttrium-90 radioembolization. Currently, physicans use a special scan to figure out if some of the treatment might accidentally go to the lungs, but that step adds extra time, cost, and risk. We are testing whether a regular contrast CT, something patients already get, can give us the same information. The use of just the CECT scan will make the process safer, quicker, and easier on both patients and providers.

#8 UC DAVIS SUSPICION OF CANCER CLINIC: A NOVEL CLINICAL PATHWAY TO ENHANCE ACCESS TO CANCER DIAGNOSIS

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Abstract
Background: The UC Davis Comprehensive Cancer Center (UCDCCC) is a matrix cancer center, which has clinical services embedded within a larger health system. Oncologists are subspecialized by cancer type and typically require a tissue diagnosis to provide care. Patients who present with conditions suspicious for cancer but without a diagnosis may face access issues and delays in care, especially if their primary care is external to UCD as UCDCCC serves a large, diverse catchment area. In October 2022, the UCDCCC established a Suspicion of Cancer (SOC) clinic, in collaboration with the

UCD Division of General Internal Medicine, in order to facilitate outpatient care. This study describes SOC implementation and early outcomes.

Methods: The SOC clinic is staffed 3 half-days per week by a general medicine physician. Eligible patients were referred by both internal (outpatient, emergency department, hospital) and external (outpatient) sources to UC Davis. Patient referrals were triaged by the SOC physicians and designated triaging oncologists; diagnostic modalities ordered or coordinated included imaging, blood tests and tissue biopsy; and if cancer was confirmed, patients were referred to oncology. Over 2022-2024, data were tracked and descriptive statistics used to analyze number of new patients, referral source, referral reason, and outcomes of diagnostic work-up. Seven patients who were referred to the clinic for survivorship care were excluded.

Results: Over a two-year period, the SOC clinic saw 289 new patients. The leading referral source was from outpatient providers (65%), both internal and external to UC Davis. Other referral sources included the ED (20%), followed by inpatient providers (15%). The leading referral reasons were soft tissue and organ masses (55%), lymphadenopathy (21%), and bone lesions (14%). For patient outcomes, approximately 45% received a diagnosis of cancer, 38% were confirmed not to have cancer, 10% were still undergoing evaluation, and 7% were lost to follow up.

Discussion/Limitations: The SOC clinic has been successful to facilitate diagnosis and access to cancer care. Ongoing evaluation will examine patient characteristics, type of cancer including stage, and timeliness of care. Future efforts will explore improving efficiencies of referral triage or scheduling and potential expansion in the catchment area.

Lay Abstract

The Suspicion of Cancer clinic is a new clinical pathway within the UCD Comprehensive Cancer Center to provide timely access to diagnostic testing when a cancerous condition is suspected. The clinic is staffed by general internists who recommend diagnostic testing to determine a diagnosis. Clinic providers guide patients through the diagnostic process and transition them to oncologists if cancer is confirmed.

#9 COMPREHENSIVE STATE POLICIES ASSOCIATED WITH HIGHER TOBACCO TREATMENT DELIVERY IN U.S. SUBSTANCE USE DISORDER TREATMENT FACILITIES

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Abstract

Background: Over 70% of adults with a substance use disorder (SUD) use tobacco, and individuals receiving SUD treatment are nearly twice as likely to die of tobacco-related disease (including cancer) than the general population. Integrating tobacco cessation services into SUD treatment may reduce tobacco-related health disparities and improve treatment outcomes among people with behavioral health conditions. To address this need for integrated care, 5 states have implemented policies requiring SUD facilities to provide tobacco treatment, 15 states require tobacco-free grounds, and 4 states have both policies.

Objective: This study assessed whether state policies requiring SUD facilities to provide tobacco treatment and/or tobacco-free grounds were associated with SUD facilities reporting delivery of tobacco screening and cessation treatment (TSC).

Methods: Using cross-sectional data from the 2023 National Substance Use and Mental Health Services Survey and statewide legislative data from the Public Health Law Center, we created a four-category exposure variable to describe state tobacco control policies in SUD facilities: states that (1) have no tobacco-free grounds or treatment policy, (2) require only tobacco-free grounds, (3) require only tobacco treatment, and (4) require both tobacco-free grounds and

tobacco treatment. To compare the proportion of facilities that provide TSC in these policy groups, we employed Poisson regression models with a robust error variance.

Results: Among 13,609 facilities, 89% provided any TSC, including 83% providing tobacco screening and 76% providing tobacco cessation treatment. States with policies that require only tobacco treatment (PR = 1.02, 95% CI = 1.01, 1.04) or treatment and tobacco-free grounds (PR = 1.09, 95% CI = 1.08, 1.11) had a higher proportion of facilities reporting TSC, compared to facilities with no state tobacco-free grounds or treatment policies. There was no evidence of an association between having a state policy for only tobacco-free grounds and an increased reporting of TSC.

Conclusion: Comprehensive policies that promote both tobacco treatment and tobacco-free grounds in SUD facilities may improve TSC delivery in the behavioral health population, which will ultimately improve health outcomes. Future efforts will adjust for state- and facility-level factors to determine the adjusted prevalence ratios.

Lay Abstract

Over 70% of adults with a substance use disorder (SUD) use tobacco, and individuals receiving SUD treatment are nearly twice as likely to die of tobacco-related disease (including cancer) than the general population. Integrating tobacco cessation services into SUD treatment may reduce tobacco-related health disparities and improve treatment outcomes among patients in addiction treatment. To address this need for integrated care, 5 states have implemented policies requiring SUD facilities to provide tobacco treatment, 15 states require tobacco-free grounds, and 4 states have both policies. This study assessed whether state policies requiring SUD facilities to provide tobacco treatment and/or tobacco-free grounds were associated with SUD facilities reporting delivery of tobacco screening and cessation treatment (TSC). Using data from the 2023 National Substance Use and Mental Health Services Survey and statewide legislative data from the Public Health Law Center, we categorized SUD facilities into the following tobacco control state policy groups: states that (1) have no tobacco-free grounds or treatment policy, (2) require only tobacco-free grounds, (3) require only tobacco treatment, and (4) require both tobacco-free grounds and tobacco treatment. We then compared the proportion of facilities that provide TSC in these policy groups. States with policies that required only tobacco treatment or treatment and tobacco-free grounds had a higher proportion of facilities reporting TSC compared to states without tobacco-free grounds or treatment policies. States with a policy for only tobacco-free grounds did not have an increased proportion of facilities reporting TSC. Comprehensive policy approaches that promote both tobacco treatment and tobacco-free grounds in SUD facilities may improve TSC delivery in addiction treatment, which will ultimately improve health outcomes.

#10 HIGH MOBILITY GROUP A1 (HMGA1) REGULATES HIGH-GRADE SOFT TISSUE SARCOMA (STS) CANCER STEM CELLS (CSC) AND METASTATIC CELL BEHAVIORS

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Abstract

Sarcomas encompass a group of rare and heterogenous tumors of mesenchymal origin. Despite aggressive treatment with surgery, radiation and chemotherapy, sarcomas have a high rate of recurrence and metastasis with most patients developing lung metastasis. Those with metastasis have a dismal 30% survival rate at 3 years. Our lab has created a spontaneous metastasis model which allows for a critical comparison between primary tumor and lung metastatic lesions. In this model, tumors are injected into the calf of mice and then metastasize to the lung, mimicking the human disease. Differential expression analysis comparing genes upregulated in the metastatic sample as compared to the primary tumor revealed HMGA1 as significantly enriched in metastatic lesions. Across sarcoma samples in the cancer genome atlas (TCGA) high expression of HMGA1 is correlated with poor overall survival. CSCs are a small population of

cells within the tumor that can drive disease recurrence, chemoresistance, and metastasis. HMGA1 is an epigenetic regulator that has been shown to affect the CSC population and metastasis across cancer types. We hypothesize that HMGA1 promotes high-grade STS pulmonary metastasis by maintaining the CSC population.

To understand whether HMGA1 regulates sarcoma CSCs to promote metastasis, we used two short hairpin RNAs (shRNAs) to knockdown the expression of HMGA1 in our metastatic cell line. We then assessed CSC properties using spheroid formation assays and aldehyde dehydrogenase assays (ALDH). This revealed that loss of HMGA1 reduces CSC properties. To identify how HMGA1 is maintaining the CSC population we investigated other genes that were upregulated in the lung metastatic lesions and had CSC associations. SRY- box 9 (SOX9) was identified as a potential candidate. Western and RT-PCR analysis of metastatic sarcoma cell lines demonstrated that loss of HMGA1 reduces SOX9 expression. In addition, overexpression of HMGA1 increases SOX9 expression in parental sarcoma cell lines. Finally, we investigated the effects of HMGA1 on metastatic cell behaviors like proliferation, migration, and invasion in vitro. This revealed that loss of HMGA1 reduces metastatic cell behaviors suggesting a critical role during sarcoma metastasis. Understanding how HMGA1 promotes high-grade STS pulmonary metastasis will create new therapeutic opportunities for this devastating disease.

Lay Abstract
My research focuses on understanding what makes soft tissue sarcomas metastasize to the lungs.

#11 METABOLIC REPROGRAMMING IN KIDNEY CANCER: THE ROLE OF S-ADENOSYLMETHIONINE IN TUMOR PROGRESSION

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Abstract
Metabolic reprogramming is a hallmark of cancer, driving proliferation and metastasis. Methylthioadenosine phosphorylase (MTAP), a key enzyme in S-adenosylmethionine (SAM) metabolism, is deleted in approximately 15% of cancers, contributing to immune evasion and poor prognosis. However, the role of SAM in cancer progression remains unclear. To address this, we analyzed SAM-correlated metabolites in kidney cancer patient samples and identified four key metabolic pathways associated with SAM: fructose and mannose metabolism, purine metabolism, alanine, aspartate, and glutamate metabolism, and branched-chain amino acid (BCAA) biosynthesis. Fructose metabolism promoted the Warburg effect and carcinogenesis via uric acid production, while purine biosynthesis facilitated immune evasion and metabolic adaptation through AMPK-mTOR signaling. Additionally, aspartate and glutamate supported tumor proliferation via mitochondrial functions, and BCAA biosynthesis enhanced tumor growth and immune suppression via mTOR and BCAT1 activation. These findings highlight SAM as a central regulator of metabolic pathways in kidney cancer and suggest potential therapeutic targets for intervention.

Lay Abstract
Certain cancers are deficient of MTAP, a vital enzyme, which causes an accumulation of SAM, another important compound. With the accumulation of SAM, there is increased growth of cancer and risk of fatality for the patient. To understand why this is, we looked at numerous metabolic pathways including fructose and mannose metabolism, purine metabolism, alanine, aspartate, and glutamate metabolism, and branched-chain amino acid (BCAA) biosynthesis. As we examined these pathways, we highlighted specific genes and components of the pathways that led to either carcinogenesis, the initiation of cancer formation, or increased tumor growth. These correlated pathways allowed us to understand why the accumulation of SAM leads to cancer cell proliferation and metastasis.